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POSTER PRESENTATION

Does PCSK9 antibody therapy lower circulating interleukin-6? A systematic review and meta-analysis of controlled studies

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SMD −0.37
lower circulating IL-6 than control, $p < 0.001$

−0.62
largest reduction, acute cerebrovascular disease

1677 patients
12 controlled studies, 13 treatment arms

Robust
stable on leave-one-out, no publication bias

BACKGROUND

Interleukin-6 (IL-6) is a central upstream cytokine in atherosclerosis. It drives the hepatic acute-phase response, promotes endothelial dysfunction and contributes to plaque instability, and genetic and trial evidence has placed the IL-6 pathway on the causal path to atherothrombotic events. PCSK9 monoclonal antibodies lower LDL cholesterol by 50 to 70 percent beyond statin therapy and reduce cardiovascular events, and preclinical work suggests PCSK9 also has LDL-independent pro-inflammatory actions. Whether PCSK9 antibody therapy translates into lower circulating IL-6 in patients is unresolved: individual studies have reported reductions, no change, and occasional increases, in populations that differ widely in baseline inflammatory burden. We therefore pooled the available controlled clinical evidence.

METHODS

PubMed, Scopus, Web of Science and the Cochrane Library were searched from inception to July 2026 for controlled clinical studies of PCSK9 monoclonal antibodies that reported circulating IL-6 in adults with established cardiovascular or cerebrovascular disease. Two reviewers screened records, extracted data and appraised each study independently, with disagreements resolved by consensus. Standardized mean differences (SMD) with 95% confidence intervals were pooled under a DerSimonian and Laird random-effects model in Comprehensive Meta-Analysis v3, and heterogeneity was quantified with the I^2 statistic. Risk of bias was assessed with RoB 2 for randomized trials and ROBINS-I for non-randomized studies. Publication bias was examined by funnel plot inspection together with Egger and Begg tests, robustness by leave-one-out analysis, and certainty of evidence by GRADE. Subgroups were prespecified for clinical condition, antibody type, regimen, number of injections, treatment duration and study design.

SUBGROUP ANALYSES

Subgroup	Arms	SMD	p
Acute cerebrovascular disease or stroke	3	−0.615	< 0.001
Acute coronary syndrome	5	−0.365	< 0.001
Stable coronary artery disease	5	−0.190	0.038
Evolocumab	7	−0.393	0.004
Alirocumab	1	−0.379	0.400
Mixed alirocumab and evolocumab	3	−0.409	0.077
RG7652	2	−0.218	0.194
Single-dose regimen	2	−0.483	< 0.001
Multiple-dose regimen	11	−0.349	< 0.001
Follow-up ≤ 30 days	4	−0.429	< 0.001
Follow-up 31 to 90 days	2	−0.059	0.530
Follow-up > 90 days	7	−0.533	< 0.001
Randomized controlled trials	8	−0.356	0.011
Non-randomized studies	5	−0.399	0.006

Counts are treatment arms, not unique studies. Subgroup contrasts are exploratory and confounded.

RESULTS

The search returned 1946 records, of which 12 controlled clinical studies published between 2017 and 2026, contributing 13 treatment arms and 1677 unique participants, met the eligibility criteria. Pooled across all arms, PCSK9 monoclonal antibody therapy was associated with significantly lower circulating IL-6 than control (SMD −0.37, 95% CI −0.56 to −0.19, $p < 0.001$), with moderate to substantial heterogeneity ($I^2 = 69.0\%$, $Q = 38.77$, $p = 0.0001$). Leave-one-out analysis altered neither the direction nor the magnitude nor the significance of the pooled estimate, the funnel plot was reasonably symmetric, and neither Egger regression ($p = 0.93$) nor the Begg rank correlation test ($p = 0.95$) indicated publication bias, although both tests are underpowered with so few studies.

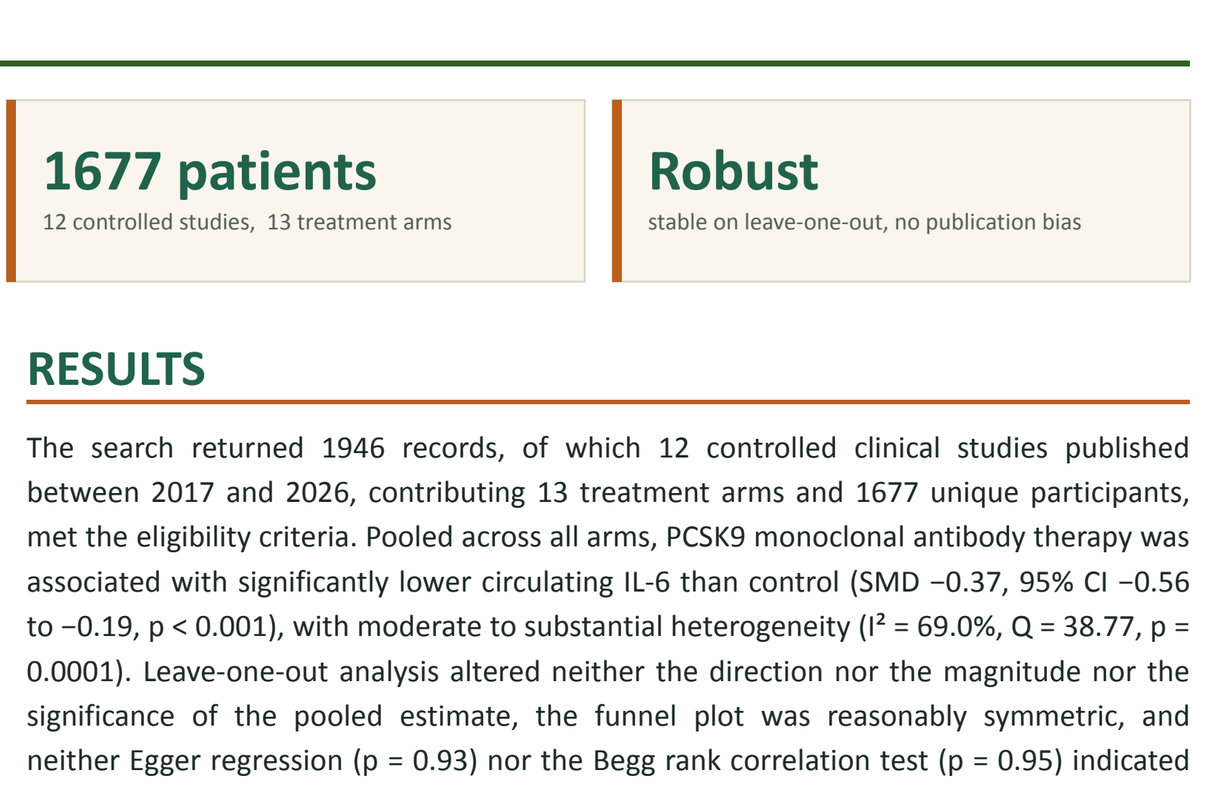


Figure 1. Random-effects forest plot of the standardized mean difference in circulating IL-6, PCSK9 monoclonal antibody therapy versus control, across 13 treatment arms.

RISK OF BIAS AND CERTAINTY

All seven randomized controlled trials were judged to raise some concerns overall, most often for selection of the reported result, missing outcome data or deviations from intended interventions. All five non-randomized studies were at serious overall risk of bias, driven in every case by confounding. GRADE certainty for the primary outcome was rated low, downgraded one level for risk of bias and one level for inconsistency.

STRENGTHS AND LIMITATIONS

Strengths include a prespecified PICOS framework, duplicate screening, extraction and appraisal, formal RoB 2, ROBINS-I and GRADE assessment, and a leave-one-out robustness check. The main limitations are the small number of eligible studies, the inclusion of non-randomized evidence at serious risk of bias, variation in IL-6 assays, sampling times and background lipid-lowering therapy, and reliance on a surrogate biomarker rather than a clinical endpoint.

CONCLUSIONS

PCSK9 monoclonal antibody therapy is associated with a modest reduction in circulating IL-6, most pronounced in acute inflammatory settings such as stroke and acute coronary syndrome and smallest in stable coronary artery disease. The certainty of this evidence is low, the subgroup contrasts are hypothesis-generating rather than confirmatory, and IL-6 is a surrogate biomarker: these data do not by themselves establish reduced vascular inflammation, plaque stabilization or clinical benefit. Adequately powered randomized trials with standardized inflammatory assessment and prespecified IL-6 endpoints are needed before an anti-inflammatory contribution to the clinical effect of PCSK9 antibodies can be claimed.

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